

## WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.\**

*The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

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\*[https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[TB308 trade name]†

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains isoniazid 100 mg.

*Excipients with potential clinical effect:*

Each tablet contains 69 mg of mannitol.

For a full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

White to off-white, capsule shaped, biconvex, beveled edge tablet debossed with **M** on one side of the tablet and **IS** on the left side of the score and **7** on the right side of the score on the other side.

The tablet can be divided into equal halves.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[TB308 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis*, including in regimens for drug-resistant tuberculosis.

It is also indicated as monotherapy or with other medicines for the prevention of tuberculosis in persons at risk.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

### 4.2 Posology and method of administration

For oral use.

#### *Posology*

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

#### **Treatment of drug-susceptible tuberculosis**

Fixed dose combination products should be used for treatment whenever possible. Only when these are not available or not suitable may single-component isoniazid 100 mg tablets such as [TB308 trade name] be given as part of a combination regimen. The duration of treatment, and the other medicines given, depend on the selected regimen.

The typical recommended dose of isoniazid is 10 mg/kg daily in patients up to 14 years of age (range 7 to 15 mg/kg daily, with the higher part of the range applying to younger children), and 4-6 mg/kg daily for older adolescents and adults.

For tuberculous meningitis different dosing regimens may apply, as recommended in WHO guidelines.

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† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

### Treatment of drug resistant tuberculosis

High-dose isoniazid may be considered as a component of a 9-month combination regimen with other tuberculosis medicines including bedaquiline, to treat drug resistant tuberculosis.

The typical recommended dose of isoniazid in such regimens is 10-15 mg/kg body weight daily in patients weighing at least 46 kg. An alternative formulation supplying higher doses of isoniazid should be used in these patients, to avoid excessive pill burden.

In patients weighing less than 46 kg the typical recommended dose is 15-20 mg/kg daily. The dose is taken once daily, as follows:

| Patient's weight      | Daily dose of isoniazid | Number of tablets of [TB308 trade name] |
|-----------------------|-------------------------|---|
| 3 to less than 5 kg   | 50 mg                   | 0.5*                                    |
| 5 to less than 7 kg   | 100 mg                  | 1*                                      |
| 7 to less than 10 kg  | 150 mg                  | 1.5*                                    |
| 10 to less than 16 kg | 200 mg                  | 2                                       |
| 16 to less than 24 kg | 300 mg                  | 3 <sup>†</sup>                          |
| 24 to less than 36 kg | 400 mg                  | 4                                       |
| 36 to less than 46 kg | 450 mg                  | 4.5 <sup>†</sup>                        |

\*A dispersible tablet formulation may be preferred where available.

<sup>†</sup>Consider use of alternative formulations containing more isoniazid.

### Prevention of tuberculosis

#### *Isoniazid monotherapy*

Isoniazid may be given daily for 6 or 9 months in the prevention of tuberculosis. Doses depend on age:

- 10 years and older: 5 mg/kg/day
- Less than 10 years: 10 mg/kg/day (range, 7–15 mg/kg)

The following daily doses of [TB308 trade name] by weight band may be used in those aged less than 10 years:

| Patient's weight      | Daily dose of isoniazid | Number of tablets of [TB308 trade name] |
|-----------------------|-------------------------|---|
| 4 to less than 8 kg   | 50 mg                   | 0.5                                     |
| 8 to less than 12 kg  | 100 mg                  | 1                                       |
| 12 to less than 16 kg | 150 mg                  | 1.5                                     |
| 16 to less than 25 kg | 200 mg                  | 2                                       |
| 25 kg or more         | 300 mg                  | 3*                                      |

\*A formulation supplying 300 mg isoniazid may be preferred, to reduce the number of tablets taken.

#### *Isoniazid with rifampicin*

Isoniazid may also be given in the same doses as for monotherapy, together with daily rifampicin, in a 3-month regimen for prevention of tuberculosis:

| Age                | Daily dose of isoniazid          | Concomitant daily dose of rifampicin |
|--------------------|----------------------------------|--------------------------------------|
| 10 years and older | 5 mg/kg                          | 10 mg/kg                             |
| Less than 10 years | 10 mg/kg/day (range, 7–15 mg/kg) | 15 mg/kg (range 10-20 mg/kg)         |

[TB308 trade name] may be used with rifampicin where appropriate doses can be given and if a suitable fixed dose combination product is not available.

### *Isoniazid with rifapentine*

Isoniazid can be given weekly or daily in combination with rifapentine, but formulations containing more isoniazid should be used in older patients rather than [TB308 trade name]. The appropriate dose and regimen depends on age and body weight. Doses are given below for reference.

#### Age over 14 years

For patients aged over 14 years, other formulations supplying higher amounts of isoniazid should be preferred. The recommended **weekly** dose is 900 mg isoniazid together with 900 mg rifapentine, taken once a week for 3 months (12 doses).

For patients 13 years of age or over, isoniazid may also be given in a **daily regimen** with rifapentine, but other formulations supplying higher amounts of isoniazid should be preferred. The recommended dose is 300 mg of isoniazid together with 600 mg of rifapentine taken once a day for 28 days.

#### Age 2–14 years

For patients aged between 2 and 14 years, the following **weekly** dose should be taken for 3 months (12 doses):

| Patient's weight      | Weekly dose of isoniazid | Number of tablets of [TB308 trade name] | Concomitant weekly dose of rifapentine |
|-----------------------|--------------------------|---|--|
| 10 to less than 16 kg | 300 mg                   | 3*                                      | 300 mg                                 |
| 16 to less than 24 kg | 500 mg                   | 5                                       | 450 mg                                 |
| 24 to 30kg            | 600 mg                   | 6*                                      | 600 mg                                 |
| Over 30 kg            | 700 mg                   | 7                                       | 750 mg                                 |

\*A formulation supplying 300 mg isoniazid may be preferred, to reduce the number of tablets taken.

### **Pyridoxine prophylaxis**

Pyridoxine supplementation considerably reduces the risk of developing peripheral neuropathy. Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, infants, adolescents, or individuals who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. Prophylactic pyridoxine should also be given to those taking high-dose isoniazid regimens.

Children aged under 5 years or weighing less than 25 kg should typically be given pyridoxine 12.5 mg daily. For those 5 years and over or weighing more than 25 kg, 25 mg of pyridoxine daily is recommended. Higher doses (2-5 mg/kg/day) may be given if signs of peripheral neuropathy develop.

### **Special populations**

#### *Patients with renal impairment*

No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to two-thirds of the normal daily dose may be considered in slow acetylators with severe renal impairment (ClCr <25 ml/min) or in those with signs of isoniazid toxicity (see sections 4.4 and 5.2).

#### *Patients with hepatic impairment*

Limited data indicate that the pharmacokinetics of isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of isoniazid toxicity (see section 4.4).

### **Method of administration and missed doses**

[TB308 trade name] is administered orally and should be taken on an empty stomach (at least 1 hour prior to or 2 hours after a meal).

For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB308 trade name] and reduce its effectiveness.

In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be omitted.

### 4.3 Contraindications

Isoniazid is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients
- acute liver disease, regardless of aetiology
- a history of drug-induced hepatic disease with isoniazid or any other medicine
- previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

### 4.4 Special warnings and precautions for use

#### *Hepatotoxicity*

Severe and sometimes fatal isoniazid-associated hepatitis has been reported and is thought to be caused by the metabolite diacetylhydrazine. The majority of cases occur within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Patients especially at risk for developing hepatitis include:

- older patients (hepatotoxicity is rare in those below 20 years of age and commonest in those aged over 50)
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
- patients with active chronic liver disease ([TB308 trade name] is contraindicated in those with a history of acute liver disease, see section 4.3)
- individuals with a history of drug misuse by injection.

Careful monitoring is also advised in malnourished or HIV-infected patients, those known to be slow acetylators (see section 5.2) and those taking other long-term therapy with potentially hepatotoxic medicines (see also section 4.5).

The incidence of severe hepatotoxicity can be minimised by careful monitoring of liver function with review of symptoms at monthly intervals. Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness for more than 3 consecutive days and abdominal tenderness, especially in the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly. Continued use of [TB308 trade name] in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured before patients start isoniazid therapy and then periodically throughout treatment. Liver enzyme values are often raised during isoniazid therapy. These effects on liver function are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even in the presence of continued therapy. However, if the concentration of liver enzymes exceeds 3 to 5 times the upper limit of normal, discontinuation of [TB308 trade name] should be strongly considered.

#### *Peripheral neuropathy*

Peripheral neuropathy is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, infancy, adolescence, pregnancy or breastfeeding. [TB308 trade name] should therefore be used with careful monitoring in patients with pre-existing neuropathy or conditions that may predispose to it and concomitant pyridoxine administration is advised in such cases

(see section 4.2).

#### *Other neurological conditions*

[TB308 trade name] should be used with caution in patients with seizure disorders or a history of psychosis.

#### *Cross-sensitivity*

Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.

#### *Diabetes mellitus*

Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid. Such individuals may also be at greater risk of peripheral neuropathy, see above.

#### *Renal impairment*

Patients with renal impairment, particularly those who are slow acetylators (see sections 4.2 and 5.2) may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

#### *Resistance*

Isoniazid must always be used in conjunction with adequate doses of other tuberculosis medicines. The use of isoniazid alone allows the rapid development of resistant strains.

#### *Excipients*

Each tablet contains mannitol, which may have a mild laxative effect.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

### **4.5 Interaction with other medicinal products and other forms of interaction**

When isoniazid is given to patients who inactivate it slowly or to patients receiving para-aminosalicylic acid concurrently, tissue concentrations may be enhanced, and adverse effects are more likely to appear. There may be an increased risk of liver damage in patients receiving rifampicin and isoniazid but liver enzymes are raised only transiently.

Isoniazid inhibits CYP2C19 and CYP3A4 in vitro. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

*Hepatotoxic medications:* in addition to specific interactions listed below, concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.

*Neurotoxic medications:* in addition to interactions listed below, concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.

| <b>Drugs by Therapeutic Area</b> | <b>Interaction</b>   | <b>Recommendations concerning co-administration</b> |
|----------------------------------|--|---|
| <b>INFECTION</b>                 |  |   |
| <i>Antiretrovirals</i>           |  |   |
| <b>Stavudine</b>                 | There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine (d4T). | No dose adjustment required.                        |
| <b>Zalcitabine</b>               | The clearance of isoniazid was found doubled when  |   |

| Drugs by Therapeutic Area  | Interaction   | Recommendations concerning co-administration   |
|--|---|--|
|  | zalcitabine was given in HIV-positive patients  | Concurrent use of isoniazid and zalcitabine should be monitored to ensure isoniazid effectiveness.   |
| <i>Antivirals for hepatitis C infection</i>  |   |  |
| <b>Daclatasvir</b><br><b>Elbasvir/grazoprevir</b><br><b>Glecaprevir/pibrentasvir</b><br><b>Ledipasvir/sofosbuvir</b><br><b>Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)</b><br><b>Simeprevir</b><br><b>Sofosbuvir (with or without velpatasvir, with or without voxilaprevir)</b> | Co-administration has not been studied.<br>Severe and sometimes fatal hepatitis associated with isoniazid may develop even after many months of treatment.  | Patients with current chronic liver disease should be carefully monitored.   |
| <b>ANTICONVULSANTS</b>   |   |  |
| <b>Carbamazepine</b><br><b>Phenytoin</b><br><b>Primidone</b>   | Isoniazid decreases the apparent clearance of these medicines, and therefore increases drug exposure.<br>Hepatotoxicity may increase following concurrent use with carbamazepine or phenytoin.<br>Isoniazid has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of 200 mg daily or more. | Co-administration with [TB308 trade name] should be undertaken with caution.<br>Plasma concentrations of the anticonvulsant should be determined prior to and after initiation of isoniazid therapy; the patient should be monitored closely for signs and symptoms of toxicity and the dose of the anticonvulsant should be adjusted accordingly.<br>For carbamazepine, a reduction between one-half or one-third was reported effective. |
| <b>Phenobarbital</b>   | Concurrent use with isoniazid may increase hepatotoxicity.  | Co-administration of [TB308 trade name] and phenobarbital should be undertaken with caution.   |
| <b>CARDIOVASCULAR MEDICINES</b>  |   |  |
| <b>Warfarin</b>  | Isoniazid may inhibit hepatic metabolism of warfarin.   | Monitor closely and adjust warfarin dose as needed.  |
| <b>GASTROINTESTINAL MEDICINES</b>  |   |  |
| <b>Antacids</b>  | The absorption of isoniazid is reduced by antacids.   | Antacids should not be co-administered with [TB308 trade name].  |
| <b>OPIOIDS AND ANAESTHETICS</b>  |   |  |
| <b>Enflurane</b>   | Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.   | Co-administration of [TB308 trade name] with enflurane should be avoided.  |

| Drugs by Therapeutic Area  | Interaction  | Recommendations concerning co-administration   |
|--|--|--|
| <b>Alfentanil</b>  | Isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil.  | The dose of alfentanil may need to be adjusted accordingly.  |
| <b>SEDATIVES</b>   |  |  |
| <i>Benzodiazepines, e.g.</i><br><b>Diazepam</b><br><b>Midazolam</b><br><b>Triazolam</b><br><b>Flurazepam</b><br><b>Chlorzoxazone</b> | Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations.             | Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly. |
| <b>OTHERS</b>  |  |  |
| <b>Disulfiram</b>  | Concurrent use of disulfiram together with isoniazid may result in increased incidence of adverse effects on the central nervous system. | Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB308 trade name].                                       |
| <i>Corticosteroids, e.g. prednisolone</i>  | In one study, concomitant use with isoniazid decreased isoniazid exposure by 22–30%.   | Isoniazid dosage adjustments may be required in rapid acetylators.   |
| <b>Levodopa</b>  | Isoniazid may reduce the therapeutic effects of levodopa.  |  |
| <b>Procainamide</b>  | Concomitant use with procainamide may increase the plasma concentrations of isoniazid.   | Patients should be carefully monitored for isoniazid toxicity.   |
| <b>Theophylline</b>  | Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels.                          | Theophylline plasma levels should be monitored and the dose adjusted as necessary.   |

### ***Interactions with food and drinks***

***Alcohol:*** concurrent daily intake of alcohol may result in an increased incidence of isoniazid-induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict alcohol intake (see section 4.4).

***Cheese and fish (histamine- or tyramine-rich food):*** concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or light-headedness.

### ***Interactions with laboratory tests***

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

## 4.6 Fertility, pregnancy and breastfeeding

### *Pregnancy*

Isoniazid crosses the placenta. Therefore, isoniazid should only be used in pregnant women or in women of child-bearing potential if the potential benefit justifies the potential risk to the fetus. It is considered that untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. Pyridoxine supplementation is recommended.

### *Breastfeeding*

Isoniazid passes into breast milk. In breast-fed infants whose mothers are taking isoniazid, there is a theoretical risk of convulsions and neuropathy (associated with vitamin B6 deficiency). They should therefore be monitored for early signs of these effects and consideration should be given to treating both mother and infant prophylactically with pyridoxine.

However, concentrations in breast milk are so low, that breastfeeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

### *Fertility*

There are no data on the effects of [TB308 trade name] on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be warned about the adverse reaction profile of this medicine, especially its potential for symptoms of neurotoxicity and should be advised that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

## 4.8 Undesirable effects

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects, and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. The majority of cases have occurred within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

The adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Therefore, often no frequency data can be given.

Frequencies are defined as very common ( $\geq 1$  in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1/10 000 to 1 in 1000), very rare ( $\leq 1/10$  000), 'not known'.

### **Nervous system disorders**

|                    |   |
|--------------------|---|
| <i>Very common</i> | peripheral neuropathy, usually preceded by paraesthesia of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in as many as 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see sections 4.2 and 4.4). |
| <i>Uncommon</i>    | seizures, toxic encephalopathy  |
| <i>Not known</i>   | polyneuritis, presenting as muscle weakness, loss of tendon reflexes<br>Hyperreflexia may be troublesome with doses of 10mg per kg body weight  |

### **Psychiatric disorders**

|                  |  |
|------------------|--|
| <i>Uncommon</i>  | memory impairment, toxic psychosis   |
| <i>Not known</i> | elevated mood, psychotic disorder<br>Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are |

usually reversed on withdrawal of the drug

### **Gastrointestinal disorders**

*Not known*                    nausea, vomiting, anorexia, dry mouth, epigastric distress, constipation, pancreatitis acute

### **Hepatobiliary disorders**

*Very common*                transient elevation of serum transaminases

*Uncommon*                    hepatitis

*Not known*                    acute hepatic failure, liver injury, jaundice

The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.

### **Renal and urinary disorders**

*Not known*                    dysuria

### **Metabolic and nutritional disorders**

*Not known*                    hyperglycaemia, metabolic acidosis, pellagra, pyridoxine deficiency, nicotinic acid deficiency

Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

### **General disorders**

*Not known*                    pyrexia

### **Respiratory, thoracic and mediastinal disorders**

*Not known*                    pneumonitis (allergic), interstitial lung disease

### **Blood and lymphatic system disorders**

*Not known*                    anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis, lymphadenopathy

### **Skin and subcutaneous tissue disorders**

*Rare*                                toxic epidermal necrolysis, eosinophilia systemic symptoms (DRESS)

*Not known*                    erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, rash, acne

### **Immune System Disorders**

*Not known*                    anaphylactic reactions

### **Musculoskeletal disorders**

*Not known*                    arthritis, systemic lupus erythematosus, lupus-like syndrome, rheumatic syndrome

### **Eye disorders**

*Uncommon*                    optic atrophy or neuritis

### **Ear and labyrinth disorders**

*Not known*                    deafness, tinnitus, vertigo

These have been reported in patients with end stage renal impairment

### **Reproductive system and breast disorders**

*Not known*                    gynaecomastia

### Vascular disorders

*Not known* vasculitis

### Investigations

*Not known* Anti-nuclear bodies

### Miscellaneous

Withdrawal symptoms, which may occur on cessation of treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

### **Reporting of suspected adverse reactions**

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

## 4.9 Overdose

### *Symptoms*

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations or visual disturbances occur within 30 minutes to 3 hours after ingestion. Periorbital myoclonus, tinnitus, tremor, hyperreflexia, tachycardia, arrhythmias, and rhabdomyolysis have been reported. With marked isoniazid overdoses ( $\geq 80$  mg/kg body-weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria and hyperglycaemia. The toxicity is potentiated by alcohol. Lethal doses have been reported to range between 80 and 150 mg/kg.

### *Treatment*

There is no specific antidote and management is largely symptomatic. Evacuation of the stomach and administration of activated charcoal may be considered if within a short time of ingestion and the patient is not experiencing seizures.

In the event of seizures and metabolic acidosis, pyridoxine is given intravenously at 1 g per g isoniazid; if the isoniazid dose is unknown, 5 g pyridoxine is given. In the absence of seizures, 2 to 3 g pyridoxine is given intravenously for prophylaxis. Pyridoxine should be diluted to reduce vascular irritation and is administered for 30 minutes via infusion pump or syringe pump. The dose is repeated if necessary.

Diazepam potentiates the effect of pyridoxine. A high dose of diazepam can also be tried to combat seizures if pyridoxine is unavailable. In severe cases, respiratory therapy should be instituted.

Metabolic acidosis and electrolyte disturbances should be corrected and good diuresis ensured. Haemodialysis or haemoperfusion has been used in the event of extremely severe intoxication.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, ATC Code: J04AC01

#### *Mechanism of action*

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long-chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

## 5.2 Pharmacokinetic properties

### Absorption of [TB308 trade name]

The absorption characteristics of [TB308 trade name] have been determined after administration of 300 mg tablets in healthy volunteers in the fasting state as follows:

| Pharmacokinetic variable  | Mean value* ± standard deviation |
|---|----------------------------------|
| Maximum concentration (C <sub>max</sub> ) (ng/mL)   | 8323 ± 3637                      |
| Area under the curve (AUC <sub>0-∞</sub> ), a measure of the extent of absorption (ng.h/mL) | 38063 ± 10516                    |
| Time to attain maximum concentration (t <sub>max</sub> ) (hours)                            | 0.92 ± 0.76                      |

\* arithmetic mean

### Pharmacokinetics of Isoniazid

|                               |   |
|-------------------------------|---|
| <b>Absorption</b>             |   |
| Absorption                    | After oral administration isoniazid is rapidly absorbed; peak serum concentrations is reached after 1–2 hours.  |
| Oral bioavailability          | ≥80%  |
| Food effect                   | The rate and extent of absorption are reduced when isoniazid is administered with food.   |
| <b>Distribution</b>           |   |
| Volume of distribution (mean) | 0.57 to 0.76 L/kg   |
| Plasma protein binding        | Very low (0-10%)  |
| Tissue distribution           | Readily diffuses into all tissues and fluids including the cerebrospinal fluid. Isoniazid is retained in the skin and in infected tissue; it crosses the placenta and is secreted in the milk of lactating mothers.   |
| <b>Metabolism</b>             |   |
|                               | Extensive metabolism in the mucosal cells of the small intestine and in the liver.<br>Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolizing enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes.<br>Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators. |
| <b>Elimination</b>            |   |
| Elimination half life         | in rapid acetylators about 1.2 hours and in slow acetylators about 3.5 hours  |

|           |   |
|-----------|---|
| Excretion | Up to 95% of ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid. |
|-----------|---|

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans at recommended isoniazid doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Treatment of pregnant rats with isoniazid at high dose resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis impairment was observed in treated rats.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Colloidal anhydrous silica, croscarmellose sodium, mannitol, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Do not store above 30°C. Store in the original package. Protect from light.

### 6.5 Nature and contents of container

#### *HDPE bottle*

Tablets are packed in a round wide mouth white HDPE bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad.

*Adsorbent cotton:* Well bleached cotton fibre, soft, hair like white filaments

Pack size: 100 tablets

#### *Blister pack*

Tablets are packed in clear transparent PVC/PVDC-Al blister pack of 10 tablets. Each carton box contains 10 blisters.

### 6.6 Special precautions for disposal and other handling

No special requirements

## 7. SUPPLIER

Mylan Laboratories Limited  
Plot No.564/A/22  
Road No.92, Jubilee Hills  
Hyderabad – 500096, Telengana  
India

Email: ProductSafety@viatris.com

## **8. WHO REFERENCE NUMBER (WHO Prequalification Programme)**

TB308

## **9. DATE OF PREQUALIFICATION**

26 September 2017

## **10. DATE OF REVISION OF THE TEXT**

January 2023

### **References**

*General reference sources for this SmPC include:*

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*Further references relevant to sections of the SmPC include:*

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*Detailed information on this medicine is available on the World Health Organization (WHO) website:*  
<https://extranet.who.int/pqweb/medicines>